CAGGGTCTCCCTTGCAACCTGAGGAGAGGTGCACACACTCTGAGGACCTAGGTGTGCAACCTCTGCCAGATGTGGG

GCGTGGCTACCCAGAGGCATGCCCCTCACCCAGCTCCACTGTCCCCACCTGCTGCTGCTGCTGTTGGTGCTGTCAT

GTCTGCCAGAGGCACCCTCTGCCCAGGTAATGGACTTTTTGTTTGAGAAGTGGAAGCTCTATAGTGACCAATGTCA

CCACAACCTAAGCCTGCTGCCCCCACCTACTGAGCTGGTCTGTAACAGAACCTTCGACAACTACTCCTGCTGGCCT

GACACCCCTCCCAACACCACTGCCAACATTTCCTGCCCCTGGTACCTACCTTGGTGCCACAAAGTGCAGCACCGCC

TAGTGTTCAAGAGGTGTGGGCCCGATGGGCAGTGGGTTCGAGGGCCACGGGGGCAGCCGTGGCGCAACGCCTCCCA

ATGTCAGTTGGATGATGAAGAGATCGAGGTCCAGAAGGGGGTGGCCAAGATGTATAGCAGCCAGCAGGTGATGTAC

ACCGTGGGCTACAGTCTGTCCCTGGGGGCCTTGCTCCTTGCGCTGGTCATCCTGCTGGGCCTCAGGAAGCTGCACT

GCACCCGAAACTACATCCATGGGAACCTGTTTGCGTCCTTTGTGCTCAAGGCTGGCTCTGTGTTGGTCATCGATTG

GCTGCTGAAGACACGGTACAGCCAGAAGATTGGCGATGACCTCAGTGTGAGCGTCTGGCTCAGTGACGGGGCGATG

GCCGGCTGCAGAGTGGCCACAGTGATCATGCAGTACGGCATCATACCCAACTATTGCTGGTTGCTGGTAGAGGGCG

TGTACCTGTACAGCCTGCTGAGCCTTGCCACCTTCTCTGAGAGGAGCTTCTTTTCCCTCTACCTGGGCATTGGCTG

GGGTGCGCCCCTGCTGTTTGTCATCCCCTGGGTGGTGGTCAAGTGTCTGTTTGAGAATGTTCAGTGCTGGACCAGC

AATGACAACATGGGATTCTGGTGGATCCTGCGTATTCCTGTCTTCCTGGCCTTACTGATCAATTTTTTCATCTTTG

TCCACATCATTCAACTTCTTGTGGCCAAGCTGCGTGCCCATCAGATGCACTATGCTGATTACAAGTTCCGGCTGGC

CAGGTCCACGCTGACCCTCATCCCTCTGCTGGGGGTCCACGAGGTGGTCTTTGCCTTTGTGACTGACGAGCATGCC

CAAGGCACCCTGCGCTCCACCAAGCTCTTTTTTGACCTGTTCCTCAGCTCCTTCCAGGGTCTGCTGGTGGCTGTTC

TCTACTGTTTCCTCAACAAGGAGGTGCAGGCAGAGCTGATGCGGCGTTGGAGGCAATGGCAAGAAGGCAAAGCTCT

TCAGGAGGAAAGGTTGGCCAGCAGCCATGGCAGCCACATGGCCCCAGCAGGGCCTTGTCATGGTGATCCCTGTGAG

AAACTTCAGCTTATGAGTGCAGGCAGCAGCAGTGGGACTGGCTGTGTGCCCTCTATGGAGACCTCGCTGGCCAGTA

GTCTCCCAAGGTTGGCTGACAGCCCCACCTGAATCTCCACTTGGAGCCTAGGCAGGTTGTGTTCAAGAAAGGGCCT

CAGAGGACAACCCAGAGCCAGATGCCCGGCCAAGGTTGAAGAGCCAAAGCAGCAAGACAGCAGCTTGTACTGTGCA

CACTCCCCTAACCTGTCCTAGCCTGGCACAGGCCACAGTGACAGAGTAGGGGTTGGATATGATGGAGAAGCCATGT

TATCTATGAACTCTGAGTGTTCCCATGTGTGTTGACATGGTCCCTGTACCCAGATATGTCCTTCAGTAAAAAGCTC

GAGTGGAGCTGCTGCACAGCTCGTGGACAGCAGGCTTGAAGCCCCCAGGGACGGGGTTTGGGAGGCCGGGGATGAG

CAGCACACTCAGCAGGTGGAGCGCTAGTGCAACCCAGGAAAGAA (SEQ ID NO:1)

FIGURE 1A

MPLTQLHCPHLLLLLLVLSCLPEAPSAQVMDFLFEKWKLYSDQCHHNLSLLPPPTELVCNRTFDNYSCWPDTPPNT

TANISCPWYLPWCHKVQHRLVFKRCGPDGQWVRGPRGQPWRNASQCQLDDEEIEVQKGVAKMYSSQQVMYTVGYSL

SLGALLLALVILLGLRKLHCTRNYIHGNLFASFVLKAGSVLVIDWLLKTRYSQKIGDDLSVSVWLSDGAMAGCRVA

TVIMQYGIIPNYCWLLVEGVYLYSLLSLATFSERSFFSLYLGIGWGAPLLFVIPWVVVKCLFENVQCWTSNDNMGF

WWILRIPVFLALLINFFIFVHIIQLLVAKLRAHQMHYADYKFRLARSTLTLIPLLGVHEVVFAFVTDEHAQGTLRS

TKLFFDLFLSSFQGLLVAVLYCFLNKEVQAELMRRWRQWQEGKALQEERLASSHGSHMAPAGPCHGDPCEKLQLMS

AGSSSGTGCVPSMETSLASSLPRLADSPT (SEQ ID NO:2)

FIGURE 1B

underlined = deleted in targeting construct

bold = sequence flanking Neo insert in targeting construct

```
CAGGGTCTCCCTTGCAACCTGAGGAGAGGTGCACACACTCTGAGGACCTAGGTGTGCAAC
CTCTGCCAGATGTGGGGCGTGGCTACCCAGAGGCATGCCCCTCACCCAGCTCCACTGTCC
CCACCTGCTGCTGCTGCTGTTGGTGCTGTCATGTCTGCCAGAGGCACCCTCTGCCCAGGT
AATGGACTTTTTGTTTGAGAAGTGGAAGCTCTATAGTGACCAATGTCACCACAACCTAAG
CCTGCTGCCCCCACCTACTGAGCTGGTCTGTAACAGAACCTTCGACAACTACTCCTGCTG
GCCTGACACCCCTCCCAACACCACTGCCAACATTTCCTGCCCCTGGTACCTACCTTGGTG
CCACAAAGTGCAGCACCGCCTAGTGTTCAAGAGGTGTGGGCCCGATGGGCAGTGGGTTCG
AGGGCCACGGGGGCAGCCGTGGCGCAACGCCTCCCAATGTCAGTTGGATGATGAAGAGAT
CGAGGTCCA**GAAGGGGGTGGCCAAGATGTATAGCAGCCAGCAGGTGATGTACACCGT**GGG
CTACAGTCTGTCCCTGGGGGCCTTGCTCCTTGCGCTGGTCATCCTGCTGGGCCTCAGGAA
GCTGCACTGCACCCGAAACTACATCCATGGAACCTGTTTGCGTCCTTTGTGCTCAAGGC
TGGCTCTGTGTTGGTCATCGATTGGCTGCTGAAGACACGGTACAGCCAGAAGATTGGCGA
TGACCTCAGTGTGAGCGTCTGGCTCAGTGACGGGGCGATGGCCGGCTGCAGAGTGGCCAC
AGTGATCATGCAGTACGGCATCATACCCAACTATTGCTGGTTGCTGGTAGAGGGCGTGTA
CCTGTACAGCCTGCTGAGCCTTGCCACCTTCTCTGAGAGGAGCTTCTTTTCCCTCTACCT
GGGCATTGGCTGGGGTGCGCCCCTGCTGTTTGTCATCCCCTGGGTGGTGGTCAAGTGTCT
GTTTGAGAATGTTCAGTGCTGGACCAGCAATGACAACATGGGATTCTGGTGGATCCTGCG
TATTCCTGTCTTCCTGGCCTTACTGATCAATTTTTTCATCTTTGTCCACATCATTCAACT
TCTTGTGGCCAAGCTGCGTGCCCATCAGATGCACTATGCTGATTACAAGTTCCGGCTGGC
CAGGTCCACGCTGACCCTCATCCCTCTGCTGGGGGTCCAC**GAGGTGGTCTTTGCCTTTGT**
**GACTGACGAGCATGCCCAAGGCACCCTGCGCTCCACCAAGCTCTTTTTTGACCTGTTCCT**
**CAGCTCCTTCCAGG**GTCTGCTGGTGGCTGTTCTCTACTGTTTCCTCAACAAGGAGGTGCA
GGCAGAGCTGATGCGGCGTTGGAGGCAATGGCAAGAAGGCAAAGCTCTTCAGGAGGAAAG
GTTGGCCAGCAGCCATGGCAGCCACATGGCCCCAGCAGGGCCTTGTCATGGTGATCCCTG
TGAGAAACTTCAGCTTATGAGTGCAGGCAGCAGCAGTGGGACTGGCTGTGTGCCCTCTAT
GGAGACCTCGCTGGCCAGTAGTCTCCCAAGGTTGGCTGACAGCCCCACCTGAATCTCCAC
TTGGAGCCTAGGCAGGTTGTGTTCAAGAAAGGGCCTCAGAGGACAACCCAGAGCCAGATG
CCCGGCCAAGGTTGAAGAGCCAAAGCAGCAAGACAGCAGCTTGTACTGTGCACACTCCCC
TAACCTGTCCTAGCCTGGCACAGGCCACAGTGACAGAGTAGGGGTTGGATATGATGGAGA
AGCCATGTTATCTATGAACTCTGAGTGTTCCCATGTGTGTTGACATGGTCCCTGTACCCA
GATATGTCCTTCAGTAAAAAGCTCGAGTGGAGCTGCTGCACAGCTCGTGGACAGCAGGCT
TGAAGCCCCCAGGGACGGGGTTTGGGAGGCCGGGGATGAGCAGCACACTCAGCAGGTGGA
GCGCTAGTGCAACCCAGGAAAGAA
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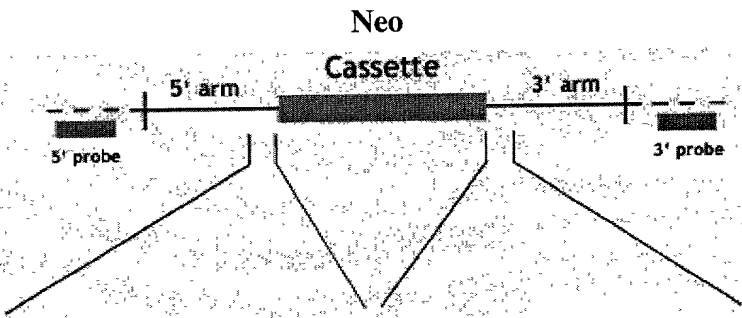
FIGURE 2A

Gene Sequence Structure *

538 bp   Sequence Deleted   1180 bp

Size of full-length cDNA: 1944 bp

Targeting Vector* (genomic sequence)

Neo
Cassette

5' arm   3' arm

5' probe   3' probe

Arm Length:
5': 3 kb
3': 0.9 kb

——— Targeting Vector
– – – – – Endogenous Locus

* Not drawn to scale

```
5'>GCAGCCGTGGCGCAACGCCTC
CCAATGTCAGTTGGATGATGAAGA
GATCGAGGTCCAGGTCAGCTCTGG
AGGGTATGGGGTGGTGTCACAGCG
GGGCTGTGTGGGGCCAGGGGATAC
GGCACTGCCCAGCCCCACTCGGCC
TCTGGTTTGCAGAAGGGGGTGGCC
AAGATGTATAGCAGCCAGCAGGTG
ACGTACACCGT<3'
  (SEQ ID NO:3)
```

```
5'>GAGGTGGTCTTTGCCTTTGTG
ACTGACGAGCATGCCCAAGGCACC
CTGCGCTCCACCAAGCTCTTTTTT
GACCTGTTCCTCAGCTCCTTCCAG
GTGAGTCTCCATCATACCCCACCC
CTGGGACCCAGAGTGCTGTCCTTG
ACCACTCTCTTTCTCCAGGGTCTG
CTGGTGGCTGTTCTCTACTGTTTC
CTCAACAAGGA<3'
  (SEQ ID NO:4)
```

FIGURE 2B

GGATCTGGCAGCGCCGCGAAGACGAGCGGTCACCGGCGCCCGACCCGAGCGCGCCCAGAGGACGGCGGGGAGCCAA

GCCGACCCCCGAGCAGCGCCGCGCGGGCCCTGAGGCTCAAAGGGGCAGCTTCAGGGGAGGACACCCCACTGGCCAG

GACGCCCCAGGCTCTGCTGCTCTGCCACTCAGCTGCCCTCGGAGGAGCGTACACACACACCAGGACTGCATTGCCC

CAGTGTGCAGCCCCTGCCAGATGTGGGAGGCAGCTAGCTGCCCAGAGGCATGCCCCCCTGCCAGCCACAGCGACCC

CTGCTGCTGTTGCTGCTGCTGCTGGCCTGCCAGCCACAGGTCCCCTCCGCTCAGGTGATGGACTTCCTGTTTGAGA

AGTGGAAGCTCTACGGTGACCAGTGTCACCACAACCTGAGCCTGCTGCCCCCTCCCACGGAGCTGGTGTGCAACAG

AACCTTCGACAAGTATTCCTGCTGGCCGGACACCCCCGCCAATACCACGGCCAACATCTCCTGCCCCTGGTACCTG

CCTTGGCACCACAAAGTGCAACACCGCTTCGTGTTCAAGAGATGCGGGCCCGACGGTCAGTGGGTGCGTGGACCCC

GGGGGCAGCCTTGGCGTGATGCCTCCCAGTGCCAGATGGATGGCGAGGAGATTGAGGTCCAGAAGGAGGTGGCCAA

GATGTACAGCAGCTTCCAGGTGATGTACACAGTGGGCTACAGCCTGTCCCTGGGGGCCCTGCTCCTCGCCTTGGCC

ATCCTGGGGGGCCTCAGCAAGCTGCACTGCACCCGCAATGCCATCCACGCGAATCTGTTTGCGTCCTTCGTGCTGA

AAGCCAGCTCCGTGCTGGTCATTGATGGGCTGCTCAGGACCCGCTACAGCCAGAAAATTGGCGACGACCTCAGTGT

CAGCACCTGGCTCAGTGATGGAGCGGTGGCTGGCTGCCGTGTGGCCGCGGTGTTCATGCAATATGGCATCGTGGCC

AACTACTGCTGGCTGCTGGTGGAGGGCCTGTACCTGCACAACCTGCTGGGCCTGGCCACCCTCCCCGAGAGGAGCT

TCTTCAGCCTCTACCTGGGCATCGGCTGGGGTGCCCCCATGCTGTTCGTCGTCCCCTGGGCAGTGGTCAAGTGTCT

GTTCGAGAACGTCCAGTGCTGGACCAGCAATGACAACATGGGCTTCTGGTGGATCCTGCGGTTCCCCGTCTTCCTG

GCCATCCTGATCAACTTCTTCATCTTCGTCCGCATCGTTCAGCTGCTCGTGGCCAAGCTGCGGGCACGGCAGATGC

ACCACACAGACTACAAGTTCCGGCTGGCCAAGTCCACGCTGACCCTCATCCCTCTGCTGGGCGTCCACGAAGTGGT

CTTTGCCTTCGTGACGGACGAGCACGCCCAGGGCACCCTGCGCTCCGCCAAGCTCTTCTTCGACCTCTTCCTCAGC

TCCTTCCAGGGCCTGCTGGTGGCTGTCCTCTACTGCTTCCTCAACAAGGAGGTGCAGTCGGAGCTGCGGCGGCGTT

GGCACCGCTGGCGCCTGGGCAAAGTGCTATGGGAGGAGCGGAACACCAGCAACCACAGGGCCTCATCTTCGCCCGG

CCACGGCCCTCCCAGCAAGGAGCTGCAGTTTGGGAGGGGTGGTGGCAGCCAGGATTCATCTGCGGAGACCCCCTTG

GCTGGTGGCCTCCCTAGATTGGCTGAGAGCCCCTTCTGAACCCTGCTGGGACCCCAGCTAGGGCTGGACTCTGGCA

CCCAGAGGCGTCGCTGGACAACCCAGAACTGGACGCCCAGCTGAGGCTGGGGGCGGGGGAGCCAACAGCAGCCCCC

ACCTACCCCCCACCCCCAGTGTGGCTGTCTGCGAGATTGGGCCTCCTCTCCCTGCACCTGCCTTGTCCCTGGTGCA

GAGGTGAGCAGAGGAGTCCAGGGCGGGAGTGGGGGCTGTGCCGTGAACTGCGTGCCAGTGTCCCCACGTATGTCGG

CACGTCCCATGTGCATGGAAATGTCCTCCAACAATAAAGAGCTCAAGTGGTCACCGTG (SEQ ID NO:5)

FIGURE 3A

MPPCQPQRPLLLLLLLLLACQPQVPSAQVMDFLFEKWKLYGDQCHHNLSLLPPPTELVCNRTFDKYSCWPDTPANTT

ANISCPWYLPWHHKVQHRFVFKRCGPDGQWVRGPRGQPWRDASQCQMDGEEIEVQKEVAKMYSSFQVMYTVGYSLS

LGALLLALAILGGLSKLHCTRNAIHANLFASFVLKASSVLVIDGLLRTRYSQKIGDDLSVSTWLSDGAVAGCRVAA

VFMQYGIVANYCWLLVEGLYLHNLLGLATLPERSFFSLYLGIGWGAPMLFVVPWAVVKCLFENVQCWTSNDNMGFW

WILRFPVFLAILINFFIFVRIVQLLVAKLRARQMHHTDYKFRLAKSTLTLIPLLGVHEVVFAFVTDEHAQGTLRSA

KLFFDLFLSSFQGLLVAVLYCFLNKEVQSELRRRWHRWRLGKVLWEERNTSNHRASSSPGHGPPSKELQFGRGGGS

QDSSAETPLAGGLPRLAESPF (SEQ ID NO:6)

FIGURE 3B

Fasting Whole Blood Glucose Results

Glucose vs. Genotype
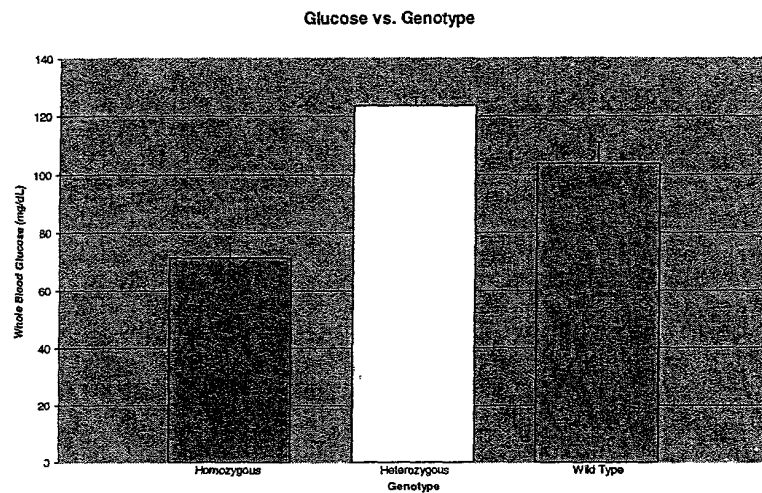
FIGURE 4

Relationship of Blood Glucose Levels to Severity of Pancreatic Lesions

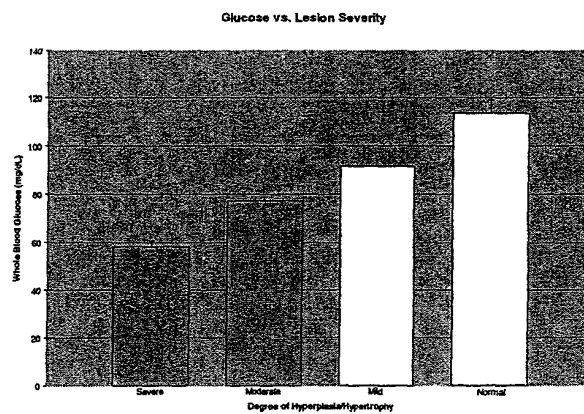**Glucose vs. Lesion Severity**
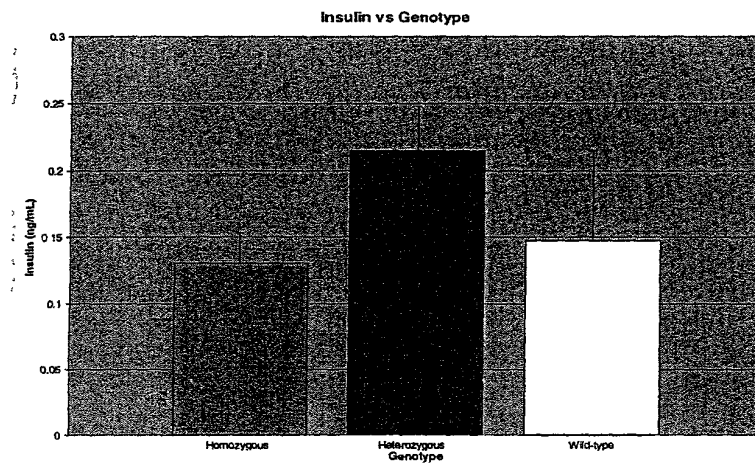

FIGURE 5

Serum Insulin Level Results

FIGURE 6

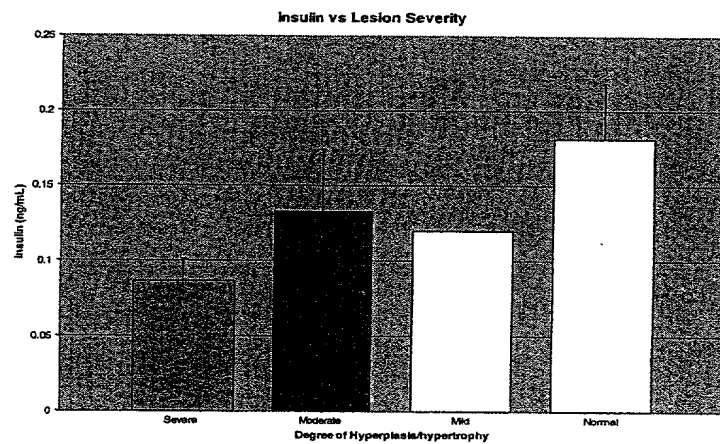# Relationship of Serum Insulin Levels to Pancreatic Lesion Severity
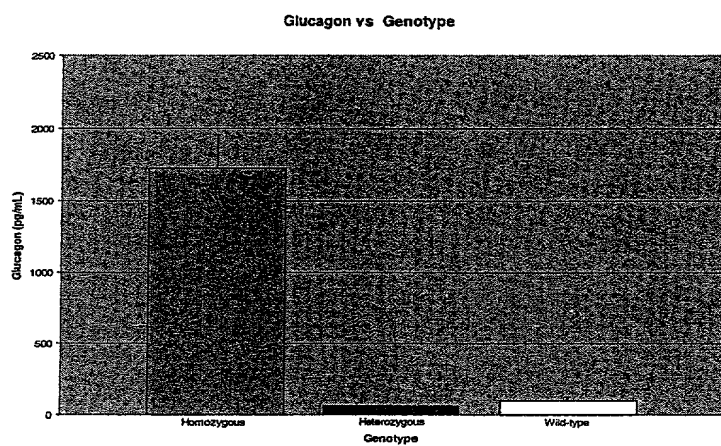

FIGURE 7

Serum Glucagon Results

Glucagon vs Genotype

FIGURE 8

Glucose Tolerance Test (I.P.)

T648 +/+
T648+/-
T648-/-

* <= 0.03
-/- v.s. +/+ or +/-
at all the time points

Blood Glucose

35
30
25
20
15
10
5
0

0   3   6   9   12   15

Minutes After Glucose
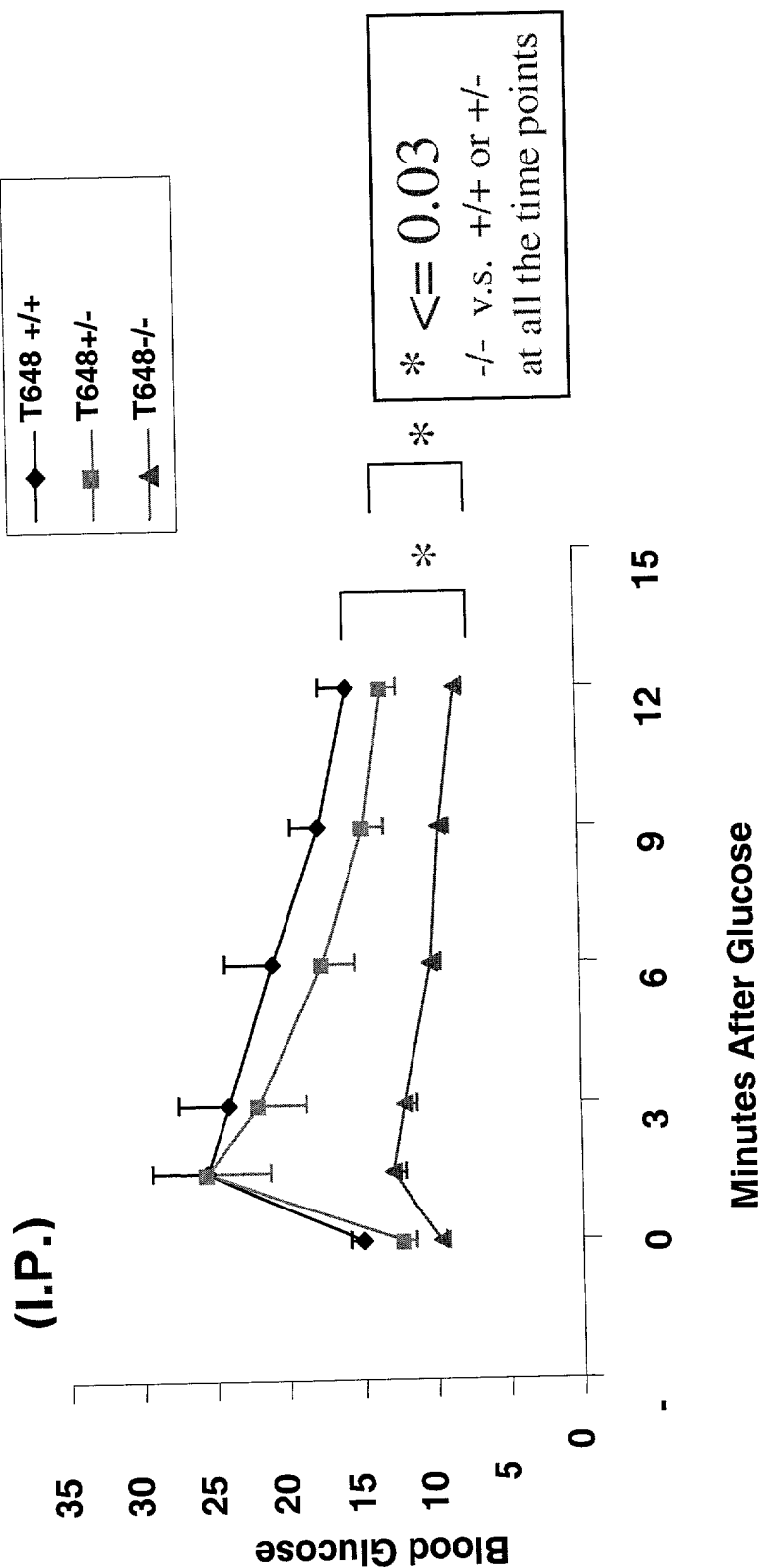
FIGURE 9

Insulin Suppression Test
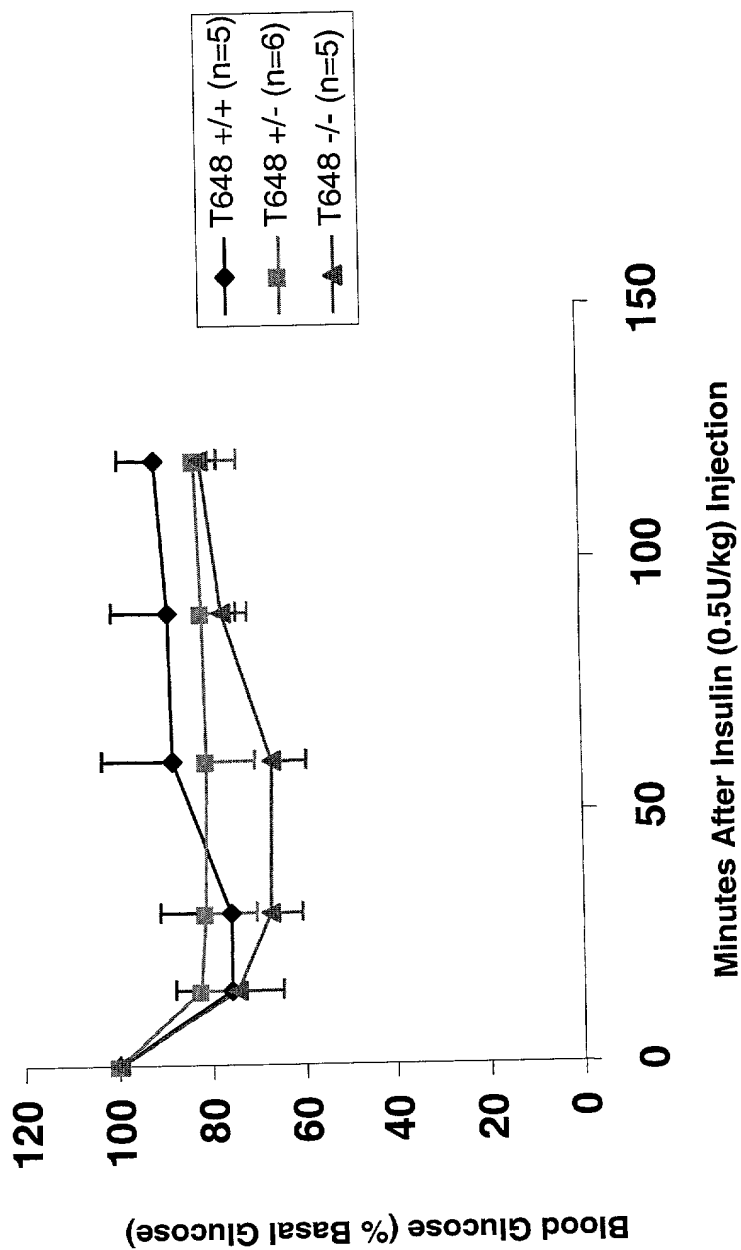
FIGURE 10

Glucose Stimulated Insulin Secretion Test

Legend:
- ■ T648+/+
- ▨ T648+/-
- ▨ T648-/-

* P = 0.01

X-axis: Minutes after Glucose Injection (0, 15)

Y-axis: Serum Insulin (ng/ml) (0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0)
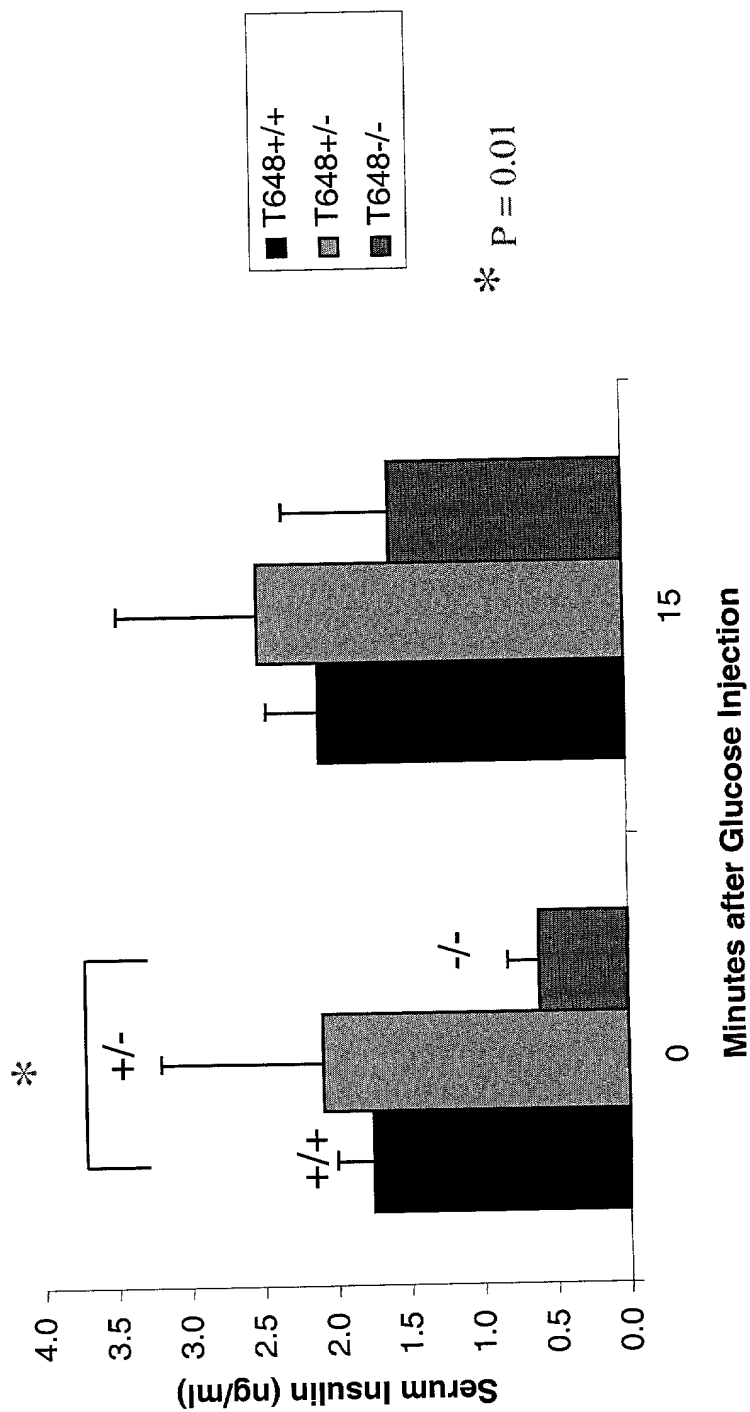
FIGURE 11

Body Weight Gain After HF Diet

FIGURE 12

Legend:
- T648 +/+
- T648+/-
- T648-/-

* $P <= 0.01$

-/- v.s. +/+ or +/-

Glucose Tolerance Test
After High Fat Diet

T648 +/+ (n=5)
T648+/- (n=5)
T648-/- (n=5)

* P <= 0.04
-/- v.s. +/+

* P <= 0.02
-/- v.s. +/-

Blood Glucose (mg/dl)

Minutes After Glucose Injection

FIGURE 13